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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,362	01/19/2001	Solomon S. Steiner	PDC 119	8907

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EXAMINER	
SHEIKH, HUMERA N	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 07/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/766,362	STEINER ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-12,14-18,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-12,14-18,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the request for extension of time (1 month-granted), the Remarks/Arguments and the Amendment, all filed 04/12/04 is acknowledged.

The 35 U.S.C. §102(b) rejections have been *withdrawn* by virtue of Amendment.

Claims 1-5, 7-12, 14-18, 20 and 21 are pending. Claims 1, 4, 5, 7, 11, 12, 14, 17 and 18 have been amended. New claims 20 and 21 have been added. Claims 6, 13 and19 have been cancelled. Claims 1-5, 7-12, 14-18, 20 and 21 are rejected.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steiner *et al.* (US Pat. No. 5,503,852).

Steiner et al. teach drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are formed in the presence of the drug to be delivered and are between 0.1 to 10 microns in diameter and whereby the

microparticles are used for diagnostic applications for imaging of the nasal tract (see reference col. 4, lines 30-55); (col. 10, lines 25-49); (col. 13, lines 13-24) and abstract.

According to Steiner, biologically active agents having therapeutic, prophylactic or diagnostic activities can be delivered and include active agents, such as hormones, vasoactive agents, anesthetics or sedatives, steroids, decongestants, antivirals, antisense, antigens, antibodies and the like (col. 10, lines 25-49).

Steiner et al. teach a system based upon diketopiperazine or one of its substitution derivatives, including *diketomorpholines and diketodioxanes*. The diketopiperazine synthetic intermediates are preferably formed by cyclodimerization to form diketopiperazine derivatives at elevated temperatures under dehydrating conditions, functionalized on the side chains, and then precipitated with drug to be incorporated into microparticles (see abstract; col. 4, lines 49-67; col. 7, lines 8-11).

The protective material, the diketopiperazines, are not biologically active and do not alter the pharmacologic properties of the therapeutic agents (col. 11, lines 1-3).

The instant invention is drawn to a composition for the nasal administration of a drug in dry powder form for administration to the nasal region, whereby the dry powder comprises microparticles having an average particle size of between 10 and 20 microns and comprising drug and diketopiperazines. There is no significant distinction observed between the instant invention and the prior art since the prior art teaches drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are between 0.1 to 10 microns in diameter and are used for nasal

applications. Hence, the instant invention is rendered unpatentable over the prior art of record.

Claims 3, 8, 10, 16, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steiner *et al.* (US Pat. No. 5,503,852) as applied to claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 above and further in view of Illum (US Pat. No. 5,690,954).

Steiner et al., as delineated above, teach drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are formed in the presence of the drug to be delivered and are between 0.1 to 10 microns in diameter and whereby the microparticles are used for diagnostic applications for imaging of the nasal tract (see reference col. 4, lines 30-55); (col. 10, lines 25-49); (col. 13, lines 13-24) and abstract.

According to Steiner et al., biologically active agents having therapeutic, prophylactic or diagnostic activities can be delivered and include active agents, such as hormones, vasoactive agents, anesthetics or sedatives, steroids, decongestants, antivirals, antisense, antigens, antibodies and the like (col. 10, lines 25-49).

Steiner et al. do not explicitly teach the selective antihistamines.

Illum ('954) teaches a drug delivery system for nasal administration of an active drug in dry powder form wherein the drug delivery system comprises microsphere particles formed of active drugs that include *antihistamines*, vasoconstrictors, anti-

inflammatory agents and anesthetics whereby the composition is administered in the form of a dry powder having a particle size of from about 10 microns to about 100 microns (see reference column 5, line 14 through col. 6, line 53); (col. 9, lines 24-61).

Suitable active drugs disclosed are anti-inflammatory agents, vasoconstrictors, anesthetics (analgesics) and antihistaminic agents. Antihistaminic agents are diphenhydramine hydrochloride, *chloropheniramine maleate* and clemastine. The microspheres are administered via the nasal route using a nasal insufflator device. Examples of these are already employed for commercial powder systems intended for nasal application (e.g., Fisons Lomudal System); (col. 8, line 44 through col. 9, line 60).

Illum teaches that the drug to be administered to a mucosal surface such as the nose, eye, etc., can be administered as a powder and can also be administered in the form of a colloidal particle comprising a microsphere system(col. 5, line 14-26).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the combined teachings of Illum within Steiner et al., because Illum teaches a nasally administered drug delivery system and device comprising various active agents that include vasoconstrictors, anesthetics (analgesics) and antihistaminic agents, among others and similarly, Steiner et al. teach drug delivery systems for the mucosal tract that comprise microparticles and microencapsulation for drugs such as vasoactive agents, anesthetics, decongestants, antivirals and the like. The expected result would be an improved and effective nasal administration microparticulate drug delivery system, as similarly desired by the Applicant.

Prior Art made of record and deemed relevant by Examiner:

US Patent No. 6,136,835 Camden 10/2000

Response to Arguments

Applicant's arguments filed 04/12/04 have been fully considered.

Firstly, Applicant argued regarding the 35 USC §102(b) rejection of claims 1-4, 7-11 and 14-17 over Illum (US Pat. No. 5,690,954) stating, "Illum does not anticipate the claimed invention for several reasons: (a) Illum requires that the microspheres be formed from a biocompatible material that will gel in contact with the mucosal surface, (b) Illum requires that the microspheres further contain an absorption enhancer; (c) Illum does not disclose the claimed narrow aerodynamic range of particle size; and (d) Illum does not disclose a diketopiperazine."

These arguments have been fully considered and were found persuasive by virtue of the current claim amendments. Accordingly, the 35 USC §102(b) rejection has been *withdrawn*. The rejections have now been reformulated as 103 Obviousness rejections only.

Next, the Applicant argued regarding the 35 U.S.C. §103(a) rejection of claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 over Steiner et al. (US Pat. No. 5,503,852) stating, "Steiner discloses several drug delivery systems using dikeopiperazines and their analogs to form microparticles encapsulating drug to be delivered. The microparticles may be microspheres with diameters ranging from 0.1 to 10 microns. Steiner does not disclose drug delivery systems for nasal

administration. Steiner does not disclose dispensing the composition using a nasal insufflator. While Steiner does mention that the microparticles can include a diagnostic imaging agent useful for imaging the nasal tract, the microparticles are administered parenterally or enterally. Steiner does not suggest microparticles having an average size of 10 to 20 microns. Steiner does not disclose nasal administration of drugs nor improvement of nasal administration. Steiner does not discuss the aerodynamic properties of the microspheres or other properties relevant to nasal administration."

These arguments have been fully considered but were not found to be persuasive. The instant claims are drawn to a composition for nasal administration of a drug in a dry powder form suitable for administration to the nasal region, the dry powder form comprising microparticles having an average particle size of between 10 and 20 microns and comprising the drug and diketopiperazines. Steiner et al. teach drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are formed in the presence of the drug to be delivered. The microparticles are used for diagnostic applications for imaging of the *nasal tract* and Steiner et al. teach that microparticles that bind to mucosal membranes are particularly preferred. Further, as the Applicant admits, Steiner et al. "does mention that the microparticles can include a diagnostic imaging agent useful for imaging the *nasal tract*". Moreover, Steiner et al. teach a microparticulate (i.e., powder) formulation and also teaches nasal tract imaging using the microparticles.

The particle size taught by Steiner et al. is between 0.1 to 10 microns in diameter. Applicants claim a particle size of between 10 and 20 microns. Hence, the 10 microns taught by Steiner et al. is an overlapping particle size, which clearly reads

on the instant particle size desired. Furthermore, one of ordinary skill in this art would be capable of determining suitable particle size ranges through the use of routine or manipulative experimentation to obtain the best possible results, as these are indeed variable parameters. The prior art teaches a similar diketopiperazine formulation used in the same field of endeavor, with a similar intended purpose and to solve the same problem as that desired by the Applicant. Hence, no significant distinction has been observed.

The argument that Steiner et al. 'do not discuss the aerodynamic properties of the microspheres or other properties relevant to nasal administration' is not persuasive since Steiner et al. recognizes microspheres having a particle size of 10 microns, and thus the specific properties (i.e., aerodynamic properties) imparted by the microspheres having a particle size of 10 microns, would also be the same. Moreover, Steiner et al. teach that the particles include a diagnostic agent that is suitable for imaging of the nasal tract.

Steiner et al. teach microencapsulation of various drugs in their diketopiperazine formulation wherein microparticles are employed for use in mucosal membrane and nasal imaging applications. Illum ('954) is relied upon for the teaching of a nasally administered dry powder formulation wherein various active agents, including antihistamines (i.e., chlorpheniramine) are contained. Illum also teaches that the microspheres can be administered via the nasal route using a nasal insufflator device (col. 9, lines 53-54).

In summary, the prior art teaches a formulation for nasal administration comprising active ingredients in combination with diketopiperazine in a similar particle size as instantly claimed. No invention is seen in the use of the instantly claimed ingredients and particle sizes, since the prior art initially recognizes and teaches a nasal formulation with the same components and similar particle sizes to achieve improved and beneficial results for drug delivery. Hence, the instant invention remains obvious and unpatentable over the prior art of record.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday through Friday from 8:00A.M. to 5:30P.M., alternate Fridays from 8:00 A.M. to 4:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

hns H.N.S.
July 12, 2004

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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